Systematic review

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A systematic review and Meta-analysis on the association between Hand-Foot Syndrome (HFS) and Cancer Chemotherapy Efficacy

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Abstract

Hand-foot syndrome (HFS) is a common skin toxicity of traditional chemotherapies. Some studies showed that HFS has an association with progression-free survival (PFS) and the overall survival (OS). So far, there is not available any systematic literature reviews or meta-analysis aimed to assess the associations between HFS, PFS and OS. For this reason, this study aims to quantitatively summarize, critically review, and interpret the recent literature related to the associations between HFS and efficacy of chemotherapy in terms of PFS and OS. Queries shaped by PICOM framework, a systematic search of three electronic databases (PubMed, Scopus, and Science Direct) was carried out for the period between January 2010 and December 2017. Quantitative data pooling was based on the calculation of Hazard Ratio (HR) with 95% Confidence Interval (95% CI) for the OS and PFS associated to the presence of HFS, through the data of original publications. Five papers were included in this systematic review for the quantitative data pooling. Patients with HFS showed improved PFS (HR = 0.532 [0.431-0.656]; p = 0.000) and improved OS (HR = 0.522 [0.427-0.638]; p = 0.000). HFS causes a reduction of compliance with oncology treatments. Healthcare providers should use this result as a trigger to foster patients' coping and the one of their family caregivers, enhancing their adherence to cancer treatments. ***Clin Ter 2019; 170(5):e388-395. doi: 10.7417/CT.2019.2165***

Key words: *Adherence, Chemotherapy, Hand-foot syndrome, Hope, Progression-free survival, Overall survival, Skin reaction*

Introduction

Hand-foot syndrome (HFS), also described as Palm-plantar erythrodysesthesia, is a common toxicity in both patients treated with some traditional chemotherapies (e.g. 5-fluorouracil, doxorubicin, cytarabine, cyclophosphamide, vinorelbine, docetaxel), and with most of the target therapies, which use epidermal growth factor receptor (EGFR) kinase inhibitors (e.g. cetuximab, erlotinib) or multi-kinase inhibitors (MKI) (e.g. sorafenib and sunitinib). The incidence of this toxicity varies from 6% to 42% depending on the type of therapy, where the factors that influence this range are mainly unknown (1–4). Further, HFS is a toxicity frequently associated with the use of oral capecitabine, affecting roughly 50% of patients, and with an incidence of grades 3-4 ranging from 10% to 20% (5). Specifically, the risk of HFS in patients treated with sorafenib seems to be seven times higher than in the control arm (6). However, there is no precise explanation for the pathogenesis of this toxicity, but the development of the syndrome appears to be associated with dose and type of drug as well as blood concentration (5). Skin reactions, which occur as paresthesias, cutaneous vesicles, hyposensitivity, appear after prolonged exposure to treatment and can increase the risk of infection as well as creating physical and emotional discomfort to the patient. Symptoms, which are typically located on the palms of the hands or feet, may occur after hours of treatment, lasting months after the last dose (7).

HFS manifestation also depends on the time of exposure to the chemotherapeutic agent, being completely reversible in most patients (1). The degree of HFS manifestation is dose-dependent and, therefore, it is often necessary to suspend or modify therapeutic dosages, due to this toxicity produces a marked decrease in quality of life and highly negatively affect the well-being of patients (3,8,9). Accordingly, many authors indicate that severe degrees of HFS may reduce compliance with oncology treatments (10). This could be associated with a lack of therapies as well as valid prevention strategies (11). For this reason, the management of HFS should be timely, because it represents a debilitating toxicity, that can lead to influence the treatment itself. Clinical evaluation plays a pivotal role at each cycle, including measures that identify and stratify patients who are at greater risk of developing HFS. The assessment of symptoms related to HFS should be done according to an appropriate staging, such as the one presented in the Common Terminology Criteria for Adverse Events version 4.0 of the National Cancer Institute (12).

Despite the adverse effects of HFS, some evidence suggest that HFS is an independent predictor of the efficacy in chemotherapies to treat various cancers (13,14). Specifically, positive associations between cutaneous toxicity and efficacy endpoints have been demonstrated, considering the

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progression-free survival (PFS) and the overall survival (OS) to determine the treatment efficacy (15,16). Also, in patients with metastatic colon carcinoma treated with capecitabine, the developing of HFS associates with improved PFS and OS (17). The same association seems to be observed also in patients with metastatic breast cancer in treatment with capecitabine (18,19). Moreover, other clinical studies show that the response rate (RR) to treatment is proportional to cutaneous toxicity, with high rates in patients who develop a higher degree of toxicity (20). It is reasonable that HFS could be interpreted as an indicator of cell activity, in fact some authors proposed HFS as a possible predictive marker of efficacy (18).

However, in the clinical practice HFS still has a role of toxicity side effect, which often induces patients to be focused only on the limitation brought by its insurgence, without considering that HFS could represent a possible predictor of efficacy, in terms of PFS and OS. So far, no recent systematic review nor meta-analysis have assessed the associations between HFS, PFS and OS and no strong evidence exists on HFS predictive role of the treatment efficacy. This information could help healthcare providers to support patients with HFS during their treatments, giving them an evidence-based information and tailored support to enhance their coping in facing with HFS to be adherent with their therapeutic protocol. For this reason, this study aims to quantitatively summarize, critically review, and interpret the recent literature related to the associations between HFS and efficacy of chemotherapy in terms of PFS and OS.

Material and methods

Search strategy

This systematic review was performed thought the systematic approach indicated by the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) statements (21), and it was consistent to the guidance of the Centre for Reviews and Dissemination (22).

Authors searched the databases PubMed, Scopus, and Science Direct for papers published between January 2000 and December 2017. The search was based on developing queries for each database and using combinations of database-specific subject headings, syntax, and Mesh terms. Each query was developed using the same Population-Intervention-Comparison-Outcome-Method (PICOM) framework (23). Adult cancer patients represented the Population, chemotherapy administration was the Intervention and Comparison, PFS and OS were the outcome, while methods were given by all the empirical studies. The principal search terms were (((cancer*) AND chemiotherap*) AND (hand-foot syndrome OR palm-plantar erythrodysesthesia)) AND (progression-free survival OR overall survival). Two authors performed the search independently, and each phase of the PRISMA flowchart (identification, screening, eligibility, and inclusion) was discussed collegially prior to move on in successive phases. The aim of the collegial discussion was the brainstorming to find agreement among authors. Inclusion criteria were: (a) empirical studies published between 2010 and 2017, (b) written in English, (c) with the availability of the abstract and (d) the full text, focused on (e) assessing HFS (f) and PFS or OS. Exclusion criteria were: (a) without the abstract and (b) the full text available, (c) with low-quality appraisal of the eligibility papers, (d) case reports (i.e. phase 3 of PRISMA, Fig. 1).

The PRISMA flowchart was used to map the number of papers identified by crossing the phases of review, which were identification, screening, eligibility, and inclusion (Fig. 1). Identification showed 956 papers from the searched databases, where 953 papers were identified from the databases consultation through the queries and three papers were identified through the reference follow-up of relevant literature. After removing duplicates, 949 papers were identified, and 12 papers were excluded using the publication data filters. Then, 937 papers were screened through the abstract/title reading by two authors independently. In this phase, 929 studies were excluded, due to they did not fit with the inclusion criteria (n= 61 excluded because the papers were not in English; n = 217 were case reports or commentaries; n= 276 were related to patients treated using radiotherapy; n = 375 did not fit with the topic of the review). Therefore, the papers in the eligibility phase were eight; their full-texts were retrieved and assessed as described below. After the appraisal only five papers were suitable for the quantitative data pooling, as described below.

Appraisal

In the eligibility phase (i.e., phase 3 of PRISMA, Fig. 1), two authors independently assessed the full-texts. The 'Joanna Briggs Institute Critical Appraisal Checklist for Randomized Controlled Trials' was used to evaluate clinical trials, while the 'The Strengthening the Reporting of Observational Studies in Epidemiology' (STROBE) checklist was used to check the reporting of cohort, case-control, and cross-sectional studies (24). At the end of the process, the two authors obtained a good inter-rater agreement related to their assessments (> .70), hence indicating that their quality appraisals were highly similar. Overall, their appraisals indicated good quality for all the eight eligible papers, which were included in the review, but three of them were not suitable for the quantitative synthesis, due to problems of sample sizing, assessment of HFS, and no evaluation of PFS and OS, as shown in Table 1. During the quality appraisal, potential disagreements were solved by discussion among authors. This approach was consistent with the recommendations of the 'Cochrane Collaboration risk of bias assessment tool' (22).

Data collection and analysis

After selecting the included papers, data were extracted in accordance with the following format: (a) authors, (b) year of publication, (c) study design, (d) sample size, (e) cancer type, (f) treatment, (g) PFS and OS, (h) association, (i) results, (l) notes on appraisal.

The outcomes considered for this meta-analysis were PFS and OS, therefore the aim was to estimate the overall strength of associations between HFS with PFS and OS,

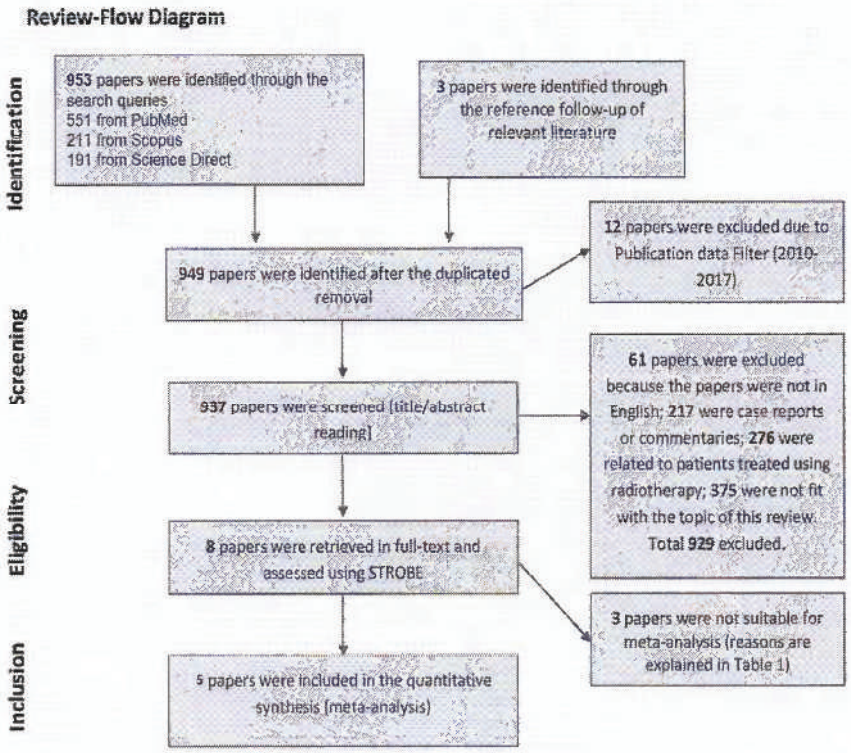

Fig. 1. Review flow diagram

using a random-effect modelling. Accordingly, we calculated Hazard Ratio (HR) with 95% Confidence Interval (95% CI) for the OS and PFS associated to the presence of HFS, through the data of original publications. The Cochrane Q, I^2 statistics and Chi square were performed to assess the heterogeneity of the included studies (25). The level of heterogeneity was acceptable, but not completely absent. For this reason, the authors ran random effect models. The software to perform data analysis was the Comprehensive Meta-Analysis (v. 2.2.057, Biostat, Englewood, USA) and the R environment (R Foundation for Statistical Computing, Vienna, Austria). In all estimates, studies were weighted according to study precision, i.e. inverse standard error of effect sizes.

Results

Description of the included studies

Only five papers were included for the quantitative data pooling (17,26–29) (Fig. 1). Specifically, as Table 1 shows, one paper had issues related to high heterogeneity in considering diverse cancer types in a limited sample (30). In another paper, the measurement of HFS was not clearly stated and it would undermine results in the data pooling (31). Further, another eligible paper did not measure neither OS nor PFS, which are necessary as outcomes in the meta-analysis (18). Finally, 5 papers were included for the quantitative synthesis.

Overall, this review encompassed a total of 1131 cancer patients to assess the association between HFS and PFS, and 1055 cancer patients to assess the association between HFS and OS. Three studies were from Germany, one from Austria and one from Japan. The used drugs were mainly bevacizumab and capecitabine. The studies enrolled patients with colon cancer (two studies), breast cancer (two studies) and pancreatic cancer (one study).

Risk of bias in included studies

The included papers mainly proposed secondary analysis on RCTs, and one retrospective analysis. Considering the paternal studies sequence generation, using random sequence generation was sufficiently clear and stated in all the method descriptions of the included RCTs. For this reason, the selection bias is low. Even the allocation of the paternal studies was clearly stated, as well as the blinding assignment to the study arms (low performance and detection bias). Missing data management were not easily deducible from the majority of the paternal studies, indicating an unclear attrition bias for the present study. Considering other possibility of

Table 1. Eligible papers description

Authors (year)	Study design	Sample (n)	Study implementation	Type of Cancer	Treatment	Associations between HFS and efficacy of chemotherapy	Notes on quality appraisal
Zielinski et al. (2016)	Secondary analysis from RCT)	277	Austria	Patients with HER2-negative locally recurrent/ metastatic breast cancer	BEV 10 mg kg 1 on days 1 and 15 plus paclitaxel 90 mgm 2 on days 1, 8, and 15, repeated every 4 weeks) or BEV–CAP (BEV 15 mg kg 1 on day 1 plus CAP 1000 mgm 2 twice daily on days 1–14, repeated every 3 weeks)	OS and HFS: HR (95% CI) = 0,417 (0.431 - 0.772); p = 0.0002 PFS and HFS: HR (95% CI) = 0.577 (0.431 - 0.772); p < 0.0001	JBI tool's assessments by the two independent authors indicated an adequate quality. For this reason, this study was included in the meta-analysis.
Kruger et al. (2015)	Secondary analysis from RCT	255	Germany	Patients with advanced pancreatic cancer	Gemcitabine (1000 mg/m² weekly 7 followed by one week rest, then weekly 3 every four weeks, in combination with erlotinib (150 mg daily)	OS and HFS: HR (95% CI) = 0.55 (0.36 - 0.84); p = 0.005 PFS and HFS: HR (95% CI) = 0.46 (0.30 - 0.69); p = <0,001	JBI tool's assessments by the two independent authors indicated an adequate quality. For this reason, this study was included in the meta-analysis.
Boers-Sonceren et al. (2014)	Phase I trial	17	The Netherlands	Ovary Cancer (9 pazients), Endometrium Cancer (4 patients) Breast Cancer (4 patients)	Pegylated liposomal doxorubicin (PLD) in combination with temsirolimus	FS and HFS: HR (95% CI)=0.100 (0.02- 0.64); p = 0.02	JBI tool's assessments by the two independent authors indicated a number of issues, despite the methodology and rationale were good. The issues were related to the (a) heterogeneity of the sample, considering the cancer types, but especially to (b) the sample sizing, which not showed sufficient power. For this reason, the authors decided to exclude this paper for the meta-analysis.
Araki et al. (2014)	Retrospective	76	Japan	Patients with HER2-positive advanced breast cancer (HER2ABC)	1250 mg once daily + capecitabine 1000 mg /m² twice daily on days 1-14, every three weeks	PFS and HFS: HR (95% CI) = 0.318 (0.178-0.569); p = 0.000	Strobe checklist assessments by the two independent authors indicated an adequate quality. For this reason, this study was included in the meta-analysis, where only PFS was used as a measure of efficacy.
Muller et al (2014)	Observational longitudinal	735	Germany	HER2-negative or -positive patients with metastatic breast cancer	Patients received oral capecitabine for 14 days of each 21-day cycle	PFS and HFS: HR (95% CI) = 0.6 (0.49-0.74); p < 0.0001	Strobe checklist assessments by the two independent authors indicated an adequate quality for methodology and rationale, but the measurement of HFS was not clearly stated and it was not the focus of the study. For both reasons, the authors agreed in excluding this study from the meta-analysis.

following table

Azuma et al. (2012)	Secondary analysis from RCT	98	Japan	Patients with metastatic breast cancer	Patients received oral capecitabine at 1650mg/m²/d (twice daily) on days 1–21 followed by a 7-d rest period for a cycle totaling 28d (Regimen A), or 2500mg/m²/d (twice daily) on days 1–14 followed by a 7-d rest period for a cycle totaling 21d (Regimen B).	Authors used the overall response rate (ORR) and disease control rate (DCR) to assess the efficacy of treatment. Therefore, there are no associations with OS and PFS	JBI tool's assessments by the two independent authors indicated an adequate quality for methodology and rationale, but there were not measure of OS nor PFS and HFS assessment was unclearly defined. For this reason, this study was excluded from meta-analysis.
Hofheinz et al. (2012)	Secondary analysis from RCTs	374	Germany	Patient with colon cancer	2500 mg /m² Capecitabine 3-weekly + oxaliplatin vs 2000 mg /m² Capecitabine 3-weekly	OS and HFS: HR (95% CI) = 0.56 (0.396 - 0.792); p = 0.004 PFS and HFS: HR (95% CI) = 0.690 (0.513 – 0.928); p = 0.004	JBI tool's assessments by the two independent authors indicated an adequate quality. For this reason, this study was included in the meta-analysis.
Stintzing et al. (2011)	Secondary analysis from RCT	149	Germany	Patient with colon cancer	Capecitabine 2500 mg/m2 n days 1–14 given in two equal amounts followed by a 1-week rest period	OS and HFS: HR (95% CI) = 0.560 (0.362 - 0.866); p = 0.005 PFS and HFS: HR (95% CI) = 0.510 (0.361 – 0.721); p = 0.004	JBI tool's assessments by the two independent authors indicated an adequate quality. For this reason, this study was included in the meta-analysis.

Legend:
Authors in Bold were included in the meta-analysis of this systematic review; PFS: Progression free survival; OS: overall survival; HR: hazard ratio; 95% CI: 95% Confidence Interval; HFS: hand foot syndrome; BEV: Bevacizumab; Cap: capecitabina

bias assessment, it was not possible to check the possibility of selective reporting in the study reports because we did not have access to the study protocols.

Associations between HFS and PFS

Heterogeneity in the effect size was present, but low (I^2 = 8.826%). In addition, the Q statistic showed that there was no significant heterogeneity in all the effect sizes. The Forest plot depicting single study effects, confidence intervals, and overall effects is showed in Figure 2. All the described effects for each study were significant. The total studies' variance was given by the variability of effect sizes between studies, showing a value equal to 0.321. Overall, patients with HFS showed improved PFS (HR = 0.532 [0.431-0.656]; p = 0.000).

Associations between HFS and OS

Heterogeneity in the effect size was not present (I^2 = 0.000%). In addition, the Q statistic showed that there was not significant heterogeneity in all the effect sizes. The Forest plot depicting single study effects, confidence intervals, and overall effects is showed in Figure 3. All the described effects for each study were significant. The total studies variance was variability of effect sizes between studies was 0.174. Overall, patients with HFS showed improved OS (HR = 0.522 [0.427-0.638]; p = 0.000).

Discussion

This systematic review showed the strengths of associations between the presence of HFS and PFS/OS in cancer patients who underwent chemotherapy treatment. To our knowledge, this study is the first meta-analysis of the available evidence on this topic. The results confirm that HFS is a positive predictor of improved PFS and OS. So far, the associations between the presence of HFS and PFS/OS in cancer patients has not been discussed considering the possible implication for healthcare practice before. The results of this study allow to confirm that the presence of HFS is associated with better PFS and OS, thus we intend to discuss this evidence in terms of implication for clinical practice, highlighting its possible meanings for cancer patients.

Skin toxicities as secondary effect of chemotherapy and specifically HFS are described as a cause of dissatisfaction, affecting quality of life and well-being of patients (3,8,9), as well as reducing their compliance with the treatments (10). However, our results – in line with the ones of the included studies (17,26–29)day 1, followed by 250 mg m(-2 – highlighted a positive meaning associated to the presence of HFS during chemotherapy, which is the relation between HFS and the efficacy of the treatment, given by the PFS (HR = 0.532 [0.431-0.656]; p = 0.000) and OS (HR = 0.522 [0.427-0.638]; p = 0.000). This information should be used to enhance patients' resources in facing the challenges of their condition.

Some authors have described how healthcare providers are strategic in enhancing cancer patients' willingness to improve their QoL, well-being and compliance (32,33), as well as to support their family caregivers (34). Our study results provide information useful to support the education of cancer patients with HFS and their family caregivers. Accordingly, the information coming from this study showing the association between HFS and PFS/OS could be used to sustain the self-management of stressful situations among cancer patients and their family caregivers using education. Overall, the associations emerged in this study could represent an important base to provide proper support and information to cancer patients with HFS, sustaining their capability to cope with the issues related to skin toxicities.

Strengths and limitations

This systematic review and meta-analysis presents a number of limitations that need to be discussed. Firstly, the samples were limited to breast, colon and pancreatic cancers, and capecitabine was the drug more described as cause of HFS. For this reason, the generalization of our results should keep into account the characteristic of the included studies, which limit the possibility of a broader inference. Another limitation is the low number of included studies, where five studies had an experimental design and one was a retrospective analysis. To manage this difference in the study design, the authors used the validated checklist for the appraisal. However, this meta-analysis was the first taking into account the associations between HFS and both PFE and OS. Thus, it could represent a starting point both for clinical practice and for future research on the topic, integrating available evidence. Further, the interpretation of results is clear, as no discordance between studies' effects were found. The relevance of this study results is related to the possibility to use the information on the associations between HFS and PFS/OS to foster patients' coping and the one of their family caregivers, enhancing their adherence to cancer treatments.

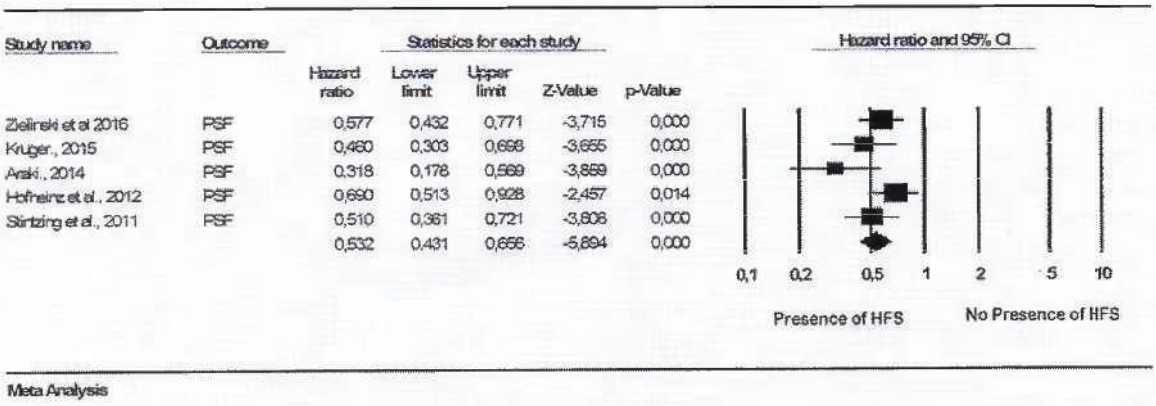

Fig. 2. Forest Plot of the meta-analysis on the associations between HFS and PSF. The size of the square represents the weight that the corresponding study exerts in the meta-analysis, while each line represents the confidence interval of an effect estimate. The pooled estimate is marked with a black diamond.

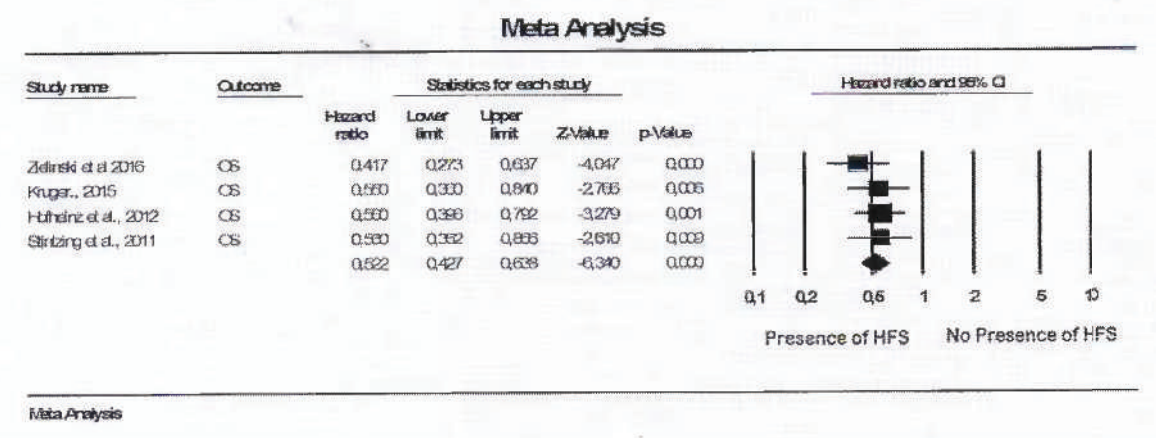

Fig. 3. Forest Plot of the meta-analysis on the associations between HFS and OS. The size of the square represents the weight that the corresponding study exerts in the meta-analysis, while each line represents the confidence interval of an effect estimate. The pooled estimate is marked with a black diamond.

Conclusion

The results of this meta-analysis suggest that cancer patients with HFS during the chemotherapy have more likelihood to have a better PFS and OS. Healthcare providers should use this result as a trigger to foster patients' hope and the one of their family caregivers, enhancing their positive coping strategies, persistence and adherence to cancer treatments. Accordingly, future research should empirically investigate the use of this evidence in clinical education and information as a hope trigger for cancer patients, reducing the negative effect of HFS on patients' QoL, wellbeing and compliance.

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